专 利 合 作 条 约

PCT

专利性国际初步报告

（PCT 第II章）

（PCT 36 和细则 70）

申请人或代理人的档案号 IEC030032PCT	关于后续行为 参见 PCT/IPEA/416 表	
国际申请号 PCT/CN2004/000842	国际申请日（日/月/年） 21.7 月 2004（21.07.2004）	优先权日（日/月/年） 22.7 月 2003（22.07.2003）
国际专利分类(IPC)或者国家分类和 IPC 两种分类 IPC7 C07K19/00 C12N15/62 A61K39/395 A61P35/00		
申请人 中国医学科学院医药生物技术研究所 等		

1. 本报告是国际初步审查单位根据条约 35 做出的国际初步审查报告，并依照条约 36 将其传送给申请人。

2. 本报告共计 5 页，包括扉页。

3. ☐ 本报告还有附件，
   a. ☐ (传送给国际局和申请人)共计 _____页，包含
      ☐修改后的并且作为本报告基础的说明书修改页、权利要求书修改页和/或附图修改页，和/或对本国际初步审查单位所做出的更正页(见 PCT 细则 70.16 和行政规程 607)。
      ☐国际初步审查单位认为修改超出原始公开范围的取代页，参见第 I 栏第 4 项和补充栏。
   b. ☐ （传送给国际局）共计 (指明电子载体的类型和数量) _____，包含有在与序列表有关的补充栏中指明的电子形式的序列表和/或与其相关的表格。（行政规程 802）

4. 本报告包括关于下列各项的内容：

   I ☒ 报告的基础

   II ☐ 优先权

   III ☒ 不做出关于新颖性、创造性和工业实用性的意见

   IV ☐ 缺乏发明的单一性

   V ☒ 按条约 35(2)关于新颖性、创造性或工业实用性的理由；支持这种意见的引证和解释

   VI ☐ 引用的某些文件

   VII ☐ 国际申请中的某些缺陷

   VIII ☐ 对国际申请的某些意见

提交要求书的日期 07.1 月 2005（07.01.2005）	完成本报告的日期 21.11 月 2005（21.11.2005）
中华人民共和国国家知识产权局 IPEA/CN 中国北京市海淀区西土城路 6 号(100088) 传真号：(86-10)62019451	受权官员 杨振宇 电话号码 (86-10)：62085073

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I. 报告的基础

1. 关于语言，本报告将基于：

☒ 申请提出时使用的语言。

☐ 该申请的_____语言译文，提供该种语言的译文是

☐ 为了国际检索而提交的译文所使用的语言（细则 12.3 和 23.1（b））。

☐ 为了国际申请的公布而提交的译文所使用的语言（细则 12.4）。

☐ 为了国际初步审查而提交的译文所使用的语言（细则55.2和/或55.3）。

2. 关于国际申请中各个部分，本报告基于（申请人为答复受理局根据条约 14 所发通知而提交的替换页，在本报告中视为“原始提交”的文件，不作为本报告的附件）

☒ 原始提交的国际申请。

☐ 说明书，第_____页 原始提交的，
第_____页 _____初审单位收到的，
第_____页 _____初审单位收到的。

☐ 权利要求，第_____页，原始提交的，
第_____页，按条约 19 条修改的(附有说明)，
第_____页 _____初审单位收到的，
第_____页 _____初审单位收到的。

☐ 附图，第_____页，原始提交的。
第_____页*，_____初审单位收到的，
第_____页*，_____初审单位收到的。

☒ 序列表和/或相关表格——参见与序列表有关的补充栏。.

3. 修改导致以下内容的删除：

☐ 说明书，第 _____页

☐ 权利要求，第 _____ _____项

☐ 附图，第 _____页，图 _____

☐ 序列表 *（具体说明）* _____

☐ 与序列表相关的表格 *（具体说明）* _____

4. ☐ 由于本报告附件的(某些)修改，如下所列，被认为超出了原始公开的范围，如补充栏所示，因此本报告是按照没有修改的情况做出的(细则 70.2(c))。

☐ 说明书，第 _____页

☐ 权利要求，第 _____项

☐ 附图，第_____页，图_____

☐ 序列表（具体说明） _____

☐ 与序列表相关的表格（具体说明）_____

*如果第 4 项适用，一些或全部的文件页可能做出“被取代”标记。

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III. 对于新颖性、创造性和工业实用性不做出审查意见

1. 对于：

☐ 整个国际申请

☒ 权利要求(编号)9

没有审查所要求保护的发明是否具有新颖性，创造性(非显而易见性)，或者工业实用性，

因为：

☒ 该国际申请，或所述权利要求(编号)9

涉及下列无须进行国际初步审查的主题(*具体说明*)：

PCT 细则 67.1（iv）规定的治疗人体或动物体的外科手术或者疗法以及诊断方法。

☐ 说明书、权利要求或者附图(下面特别指明的部分)或者所述权利要求 _____
不清楚，以致不能形成任何有意义的审查意见(*具体说明*)：

☐ 权利要求书或所述权利要求 _____ 没有得到说明书的充分支持，
以致不能形成任何有意义的审查意见。(*具体说明*)：

☐ 对权利要求 _____ 没有做出任何国际检索报告。

☐ 没有序列表，无法进行有意义的初步审查；申请人在规定的期限内：

☐ 没有提交符合《行政规程》附录 C 规定标准的纸件形式的序列表，并且国际初步审查单位也未获得形式和方式可以接受的序列表。

☐ 没有提交符合《行政规程》附录 C 规定标准的电子形式的序列表，并且国际初步审查单位也未获得形式和方式可以接受的序列表。

☐ 在答复根据细则 13 条之三.1（a）或(b)和 13 条之二的通知提交序列表时，没有缴纳所要求的后提交费用。

☐ 没有与序列表相关的表格，无法做出有意义的书面意见；申请人在规定的期限内没有提交符合行政规程附录 C 之二规定的技术要求的电子形式的表格，并且国际初步审查单位也未获得形式和方式可以接受的这种表格。

☐ 与核苷酸和/或氨基酸序列表相关的表格，如果仅以电子形式提交，不符合行政规程附录 C 之二的技术要求。

☐ 详情见补充栏。

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V. 按条约35(2)关于新颖性、创造性或工业实用性的意见；支持这种理由的引证和解释

1. 意见

新颖性(N)	权利要求 1-2，4-8	是
	权利要求 3	否
创造性(IS)	权利要求 4，5	是
	权利要求 1-3，6-8	否
工业实用性(IA)	权利要求 1-8	是
	权利要求	否

2. 引证和解释（细则70.7）

引用的对比文件：

1. 李顺强，江敏，甄永苏。抗癌抗生素力达霉素与抗IV型胶原酶单链抗体的基因工程组装融合蛋白。药学学报，2000，35（7），488-491。
2. 唐勇，甄永苏。抗IV型胶原酶单链抗体的表达及其对肿瘤细胞侵袭的抑制作用。癌症，2001，20：801-805。

独立权利要求1涉及一种强化融合蛋白。对比文件1（李顺强等），公开了一种融合蛋白，是由抗IV型胶原酶单链抗体scFv、力达霉素辅基蛋白LDP、二者之间的柔性肽间隔基GGGGS以及力达霉素活性发色团组成。权利要求1与之相比，不同之处在于含有组氨酸六聚体尾，然而组氨酸六聚体尾的作用和功能是本领域的技术人员熟知的，在先有文献中已有大量的描述。本领域的技术人员在对比文件1的基础上，很容易就能获得权利要求1所要保护的技术方案，权利要求1的方案对于本领域的技术人员而言是显而易见的。因此，权利要求1不符合PCT条约33（3）有关创造性的规定。

由于权利要求1不具备创造性，权利要求6和7所要求保护的制备药物的应用、权利要求8的药物组合物，都不具备创造性，不符合PCT条约33（3）有关创造性的规定。

从属权利要求2进一步限定了融合蛋白的编码基因的序列以及其氨基酸序列。对比文件2（唐勇等），已经公开了单链抗体scFv 3G11的基因序列。本领域的技术人员，结合对比文件1和对比文件2，简单地将抗IV型胶原酶单链抗体scFv M97替换为scFv 3G11，加上组氨酸六聚体尾，就能获得权利要求2的技术方案，权利要求2是显而易见的。因此，权利要求2不符合PCT条约33（3）有关创造性的规定。

权利要求3要求保护强化融合蛋白的制备方法。其步骤（a）、（b）都已经被对比文件1公开。因此，权利要求3不符合PCT条约33（2）有关新颖性的规定。

权利要求4和5要求保护的制备方法，其确定了Fv-LDP-AE分子重建的最佳反应条件、AE占发色团总量的百分比值，这些技术内容是现有技术中所没有的，对本领域技术人员不是显而易见的，因而具备新颖性、创造性。符合PCT条约33（2），（3）有关新颖性、创造性的规定。

权利要求1—8可以在工业中制造和使用，具有实用性，符合PCT条约33（4）关于实用性的规定。

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关于序列表的补充栏

续第 I 栏第 2 项：

1 关于本国际申请中所公开的对所要求保护的发明必要的核苷酸和/或氨基酸的序列表，本国际初步审查的建立是根据：

a. 文件的类型

☒ 序列表

☐ 与序列表相关的表格

b. 文件的形式

☒ 纸件形式

☐ 电子形式

c. 提交的时间

☒ 包含在国际申请中

☐ 以电子形式与国际申请同时提交

☐ 为了检索和/或审查的目的提交给初审单位的

☐ 以修改*的形式由初审单位在_____ 收到

2.另外，在提交了不只一个版本或副本的序列表和/或与序列表相关的表格情况下，已经提交了关于后续或附加版本与原始提交的文件相同或没有超出原始提交文件范围的声明。

3.其它意见:

*如果第一栏第 4 项适用，形成报告基础的序列表和/或相关表格可能做出“废除”标记。

Translation

PCT Application
PCT/CN2004/000842

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
IEC030032PCT		
International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/CN2004/000842	21 Jul. 2004(21.07.2004)	22 Jul. 2003(22.07.2003)

International Patent Classification (IPC) or national classification and IPC

IPC7 C07K19/00 C12N15/62 A61K39/395 A61P35/00

Applicant

INSTITUTE OF MEDICINAL BIOTECHNOLOGY, CHINESE ACADEMY OF MEDICAL SCIENCES et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

3. This report is also accompanied by ANNEXES, comprising:

   a. ☐ *(sent to the applicant and to the International Bureau)* a total of _____ sheets, as follows:

      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic _____, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

   ☒ Box No. I Basis of the report

   ☐ Box No. II Priority

   ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

   ☐ Box No. IV Lack of unity of invention

   ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   ☐ Box No. VI Certain documents cited

   ☐ Box No. VII Certain defects in the international application

   ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07 Jan. 2005 (07.01.2005)	21 Nov. 2005 (21.11.2005)

Name and mailing address of the IPEA/CN
The State Intellectual Property Office, the P.R.China,
6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China
100088
Facsimile No. 86-10-62019451

Authorized officer
YANG, Zhenyu
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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. I Basis of the report

1. With regard to the language, this report is based on:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of:

☐ international search (Rules 12.3(a) and 23.1(b))

☐ publication of the international application (Rule 12.4(a))

☐ international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☐ the description:

pages _____ as originally filed/furnished

pages * _____ received by this Authority on _____

pages * _____ received by this Authority on _____

☐ the claims:

pages _____ as originally filed/furnished

pages * _____ as amended (together with any statement)under Article 19

pages * _____ received by this Authority on _____

pages * _____ received by this Authority on _____

☐ the drawings:

pages _____ as originally filed/furnished

pages * _____ received by this Authority on _____

pages * _____ received by this Authority on _____

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/figs _____

☐ the sequence listing *(specify)*: _____

☐ any table(s) related to sequence listing *(specify)*: _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

This questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious),or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 9

because:

☒ the said international application, or the said claims Nos. 9
relate to the following subject matter which does not require an international preliminary examination *(specify)*:
See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement:

Novelty (N)	Claims	1-2,4-8	YES
	Claims	3	NO
Inventive step (IS)	Claims	4,5	YES
	Claims	1-3,6-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Documents cited in the International Search Report:

1. LI Shun-Qiang et al.: "An Engineered and Assembled Fusion Protein of Antitumor Antibiotic Lidamycin and scFv Directed against Type IV Collagenase." Acta Pharmaceutica Sinica , vol 35, no.7, July 2000, pages 488-491.
2. TANG Yong et al.: "Expression of Anti-Type IV Collagenase scFv Fragment and Inhibition of Tumor Cells Invasion." Chinese Journal of Cancer, vol 20, no 8, Aug 2001, pages 801-805.

D1 decloses an assembled fusion protein, the assembled fusion protein consist of a lida-chromophore(LDC) and a recombinant fusion protein LDP-Fv which comprise an scFv antibody against type IV collagenase, lida-protein(LDP) and the spacer GGGGS between them. The difference between D1 and claim 1 is that the assembled fusion protein of D1 do not have the 6His-Tag. The function and usage of 6His-Tag is well known by those skilled in the art. Therefore claim 1 lack an inventive step under Article 33.3 PCT.

Thus,claim 6-7,8 also do not fulfil the requirements of Article 33.3 PCT.

D2 decloses an scFv antibody against type IV collagenase named 3G11 and the gene sequence of the scFv 3G11. The scFv antibody against type IV collagenase in D1 is scFv M97, those skilled in the art can easily change the scFv M97 to scFv 3G11 and add a 6His-Tag at the end of scFv 3G11 to obtain the assembled fusion protein of claim 2. Therefore claim 2 lack an inventive step under Article 33.3 PCT.

Claim 3 relates to a method for obtaining the intensified fusion protein. The step (a) and (b) have been declosed by D1. Therefore the claim 3 is not novel and do not fulfil the requirements of Article 33.2PCT.

Claim 4 and 5 ascertained the best condition of intensification and the percentage of the active enediyne(AE). Therefore the claim 4 and 5 is novel and inventive and meet the requirement of Article 33.2 and 33.3 PCT.

Claim 1-8 are industrial applicable and meet the requirement of Article 33.4 PCT.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

   a. type of material

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material

   ☒ on paper

   ☐ in electronic form

   c. time of filing/furnishing

   ☒ contained in the international application as filed

   ☐ filed together with the international application in electronic form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment * on _____

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

**If item 4 in Box No.I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."*